This report is required by law (7 USC 2143). Failure to report according to the regulations can result in an order to cease and desist and to be subject to penalties as provided in Section 2150.

See reverse side for Additional information.

Interagency Report Control No. 0180-DOA-AN

UNITED STATES DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE

FY 2005

ANNUAL REPORT OF RESEARCH FACILITY

(TYPE OR PRINT)

1. REGISTRATION NO. 51-F-016 Cust. ID 441

FORM APPROVED OMB NO. 0549-0036

2. **HEADQUARTERS RESEARCH FACILITY** (Name and Address, as registered with USDA, include zip code)

National Institutes of Health
(b)(6), (6)(7)(C)
31 Center Drive, (b)(2)High, (b)(7)(F)
Bethesda , MD 20892

3. REPORTING FACILITY (List all locations where animals were housed or used in actual research, testing, teaching or experimentation, or held for these purposes. Attach additional sheets if necessary.)

FACILITY LOCATIONS (Sites)	
Composite includes: APF, CC, NCI, NEI, NHGRI, NHLBI, NIA, (b)(2)High, (b)(7)(F) AID (RML), NIAMS, NICHD, NIDA, NIDCD,	NIDCR, NIDDK, NIEHS, NIMH, NINDS, ORS, VRC

REPORT OF ANIMALS USED BY OR UNDER CONTROL OF RESEARCH FACILITY (Attach additional sheets if necessary or use APHIS FORM 7023A)

A. Animals Covered By The Animal Welfare Regulations	B. Number of animals being bred, conditioned, or held for use in teaching, testing, experiments, research or surgery but not yet used for such purposes.	C. Number of animals upon which teaching, research, experiments or tests were conducted involving no pain, distress or use of pain-relieving drugs.	D. Number of animals upon which experiments, teaching, research, surgery or tests were conducted involving accompanying pain or distress to the animals and for which appropriate anesthetic, analgesic or tranquilizing drugs were used.	E. Number of animals upon which teaching, experiments, research, surgery or tests were conducted involving accompanying pain or distress to the animals and for which the use of appropriate anesthetic, analgesic, or tranquilizing drugs would have adversely affected the procedures, results, or interpretation of the teaching, research, experiments, surgery or tests. (an explanation of the procedures producing pain or distress in these animals and the reasons such drugs were not used must be attached to this report.)	F. TOTAL NO. OF ANIMALS (Cols. C + D + E)
4. Dogs	41	41	159	0	200
5. Cats	14	5	0	0	5
6. Guinea Pigs	29	691	91	95	877
7. Hamsters	786	931	319	13	1263
8. Rabbits	372	259	1424	0	1683
9. Non-human Primates	1195	1503	817	48	2368
10. Sheep	35	41	41	0	82
11. Pigs	156	60	237	0	297
12. Other Farm Animals	--	--	--	--	--
Goats	0	0	0	0	0
Burro	0	0	0	0	0
Horses	0	0	0	0	0
Cattle	1	0	0	0	0
Chickens	1	52	1350	0	1402
Turkeys	1	0	0	0	0

ASSURANCE STATEMENTS

1) Professionally acceptable standards governing the care, treatment and use of animals, including appropriate use of anesthetic and tranquilizing drugs prior to, during And following actual research, teaching, testing, surgery or experimentation were followed by this research facility.

2) Each principal investigator has considered alternatives to painful procedures.

3) This facility is adhering to the standards and regulations under the Act, and it has required that exceptions to the standards and regulations be specified and explained by the principal investigator and approved by the Institutional Animal Care and Use Committee (ACUC). **A summary of all such exceptions is attached to this annual report.** In addition to identifying the IACUC approved exceptions, this summary includes a brief explanation of the exceptions, as well as the species and number of animals affected.

4) The attending veterinarian for this research facility has appropriate authority to ensure the provision of adequate veterinary care and to oversee the adequacy of other aspects of animal care and use.

CERTIFICATION BY HEADQUARTERS RESEARCH FACILITY OFFICIAL
(Chief Executive Officer or Legally Responsible Institutional Official)
I certify that the above is true, correct and complete (7 U.S.C. Section 2143)

SIG (b)(6), (6)(7)(C)	NAME AND TITLE OF C.E.O. OR INSTITUTIONAL OFFICIAL (Type or print) (b)(6), (6)(7)(C)	DATE SIGNED 11/23/05

AP (AU h is obsolete)

required by law (7 USC 2143). Failure to report according to the regulations can result in an order to cease and desist and to be subject to penalties as provided in Section 2150.

See reverse side for Additional information.

Interagency Report Control No. 0180-DOA-AN

UNITED STATES DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE

FY 2005

CONTINUATION SHEET FOR ANNUAL REPORT OF RESEARCH FACILITY

(TYPE OR PRINT)

1. **REGISTRATION NO.**
2. **51-F-016 Cust. ID 441**

FORM APPROVED
OMB NO. 0549-0036

3. **HEADQUARTERS RESEARCH FACILITY** (Name and Address, as registered with USDA, include zip code)

National Institutes of Health
Deputy Director for Intramural Research
31 Center Drive[redacted]
Bethesda , MD 20892

REPORT OF ANIMALS USED BY OR UNDER CONTROL OF RESEARCH FACILITY (Attach additional sheets if necessary or use APHIS FORM 7023A)

A. Animals Covered By The Animal Welfare Regulations 12 &/OR 13 OTHER (List by Species)	B. Number of animals being bred, conditioned, or held for use in teaching, testing, experiments, research or surgery but not yet used for such purposes.	C. Number of animals upon which teaching, research, experiments or tests were conducted involving no pain, distress or use of pain-relieving drugs.	D. Number of animals upon which experiments, teaching, research, surgery or tests were conducted involving accompanying pain or distress to the animals and for which appropriate anesthetic, analgesic or tranquilizing drugs were used.	E. Number of animals upon which teaching, experiments, research, surgery or tests were conducted involving accompanying pain or distress to the animals and for which the use of appropriate anesthetic, analgesic, or tranquilizing drugs would have adversely affected the procedures, results, or interpretation of the teaching, research, experiments, surgery or tests. (an explanation of the procedures producing pain or distress in these animals and the reasons such drugs were not used must be attached to this report.)	F. TOTAL NO. OF ANIMALS (Cols. C + D + E)
12. Goose	0	0	0	0	0
Duck	0	0	0	0	0
13. Gerbils	0	4	0	0	4
Ferrets	0	0	0	0	0
Cotton Rats	0	180	0	0	180
Squirrels	0	0	0	0	0
Pigeons	0	18	0	0	18
Frogs	53	2567	165	0	2732
Fish	0	0	0	0	163809
Other Amphibians	0	150	0	0	150
Vole	9	0	0	0	0
Mink	0	0	0	0	0
Wild Mice	75	0	0	0	0
Llama	1	0	0	0	0
Chinchillas	0	94	0	0	94

ASSURANCE STATEMENTS

1) Professionally acceptable standards governing the care, treatment a[redacted]animals, including appropriate use of anesthetic and tranquilizing drugs prior to, during And following actual research, teaching, testing, surgery or expe[redacted]e followed by this research facility.

2) Each principal investigator has considered alternatives to pai[redacted]

3) This facility is adhering to the standards and regulations [redacted]has required that exceptions to the standards and regulations be specified and explained by the principal investigator and approved by the Institutional A[redacted]Committee (ACUC). **A summary of all such exceptions is attached to this annual report.** In addition to identifying the IACUC approved exceptio[redacted]des a brief explanation of the exceptions, as well as the species and number of animals affected.

4) The attending veterinarian for this research[redacted]te authority to ensure the provision of adequate veterinary care and to oversee the adequacy of other aspects of animal care and use.

CE[redacted]N BY HEADQUARTERS RESEARCH FACILITY OFFICIAL
[redacted]ecutive Officer or Legally Responsible Institutional Official)
certify that the above is true, correct and complete (7 U.S.C. Section 2143)

SIGNATURE	NAME AND TITLE OF C.E.O. OR INSTITUTIONAL OFFICIAL (Type or print)	DATE SIGNED
[redacted](b)(6), (6)(7)(C)	[redacted](b)(6), (6)(7)(C)	11/23/05

A[redacted]
(AUG 91)

COLUMN E Explanation Form

This form is intended as an aid to completing the Column E explanation. Names, addresses, protocols, veterinary care programs, and the like, are not required as part of an explanation. A Column E explanation must be written so as to be understood by lay persons as well as scientists.

1. Registration Number: 51-F-0016

2. Number of animals used under Column E conditions in this study 20

3. Species (common name) of animals used in this study: Guinea Pig

4. Explain the procedure producing pain and/or distress, including reason (s) for species selected:

   We are studying the mechanisms of drug-induced liver disease, a toxicity that often leads to death in humans. Guinea Pigs are the animals of choice for studying the molecular basis of liver injury caused by inhalation anesthetics. No other animal is susceptible to this disease except for humans.
   From our prior studies, the guinea pigs do not appear to be in distress although their liver enzymes are elevated. We do not expect the animals to die.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results.

   Pain, stress, and distress cannot be relieved in our animal studies because any intervention may affect the normal response to drug-induced liver injury that we believe involves the synthesis of several protective factors. Our studies suggest that patients deficient in these protective factors may be highly susceptible to drug-induced liver injury and death.

EXPLANATION FOR COLUMN E LISTING

This form is intended as an aid to completing the column E explanation. Names, addresses, protocols, veterinary care programs, and the like, are not required as part of an explanation. A column E explanation must be written so as to be understood by lay persons as well as scientists.

1. Registration Number: **51-F-0016**
2. Number of animals used under Column E conditions in this study: **75** **FY 2005**
3. Species (common name) of animals used in this study: **guinea pig**
4. Explain the procedure producing pain/or distress, including reason (s) for species selected.

It is essential to study Herpes Simplex Virus-2) (HSV-2) candidate vaccines in animal models before clinical testing. No computer simulation or cell culture model has successfully mimicked the processes. Guinea pig is chosen instead of mouse because HSV-2 infection of guinea pigs causes mucocutaneous lesions as it does in humans but not in mice, so it's a much better model. There are seven possible routes of infection used to study herpes simplex virus pathogenesis in animal models. Virus can be given via the skin, ear, vagina, eye, footpad, nose, or systemically. Herpes infection at any of these sites can spread to central nervous system tissue and, if unintervened, can lead to death of the animal from HSV-induced neuritis. For this study we use the vaginal route for HSV-2 since we are interested in developing vaccines that can protect humans from genital infection of HSV-2.

Explanation of unrelieved pain or distress:
An HSV-2 vaccine can be effective in preventing acute HSV-2 infection and/or reducing recurrence. Therefore it is a necessity to monitor the guinea pigs for up to 90 days after wild-type virus challenge in order to determine the latent virus load in ganglia during latent infection. It is also important to determine the immune response of the vaccinated animals during the acute and latent phases of infection with wild-type virus. In the groups which did not receive vaccination, or in which the vaccine has low efficiency, after intravaginal infection with wild-type HSV-2 guinea pigs may develop lesions, genital vesicles, or ulcers. The animals that have severe lesions (see the description for Scores 3 and 4) also may exhibit transient systemic signs such as ruffled fur or hunched appearance, lethargy, persistent recumbency, or neurological signs. In most animals, the acute lesions and systemic signs resolve and the infection become latent. A few animals may develop persistent ulcerative lesions in the genital area. Some animals may develop hind limb paralysis due to spread of the virus to the nervous system. Due to the need to investigate the efficiency of vaccine candidates to reduce both acute and recurrent lesions, animals showing transient morbidity will not be sacrificed.

The following is a scoring system of lesions:
Score 0: No lesion
Score 1: Only redness
Score 2: Discrete vesicular lesion
Score 3: Large fused or irregular vesicular lesion
Score 4: Ulcer
Score S: Scab

Anesthetic or analgesic agents cannot be used, because these agents could attenuate the immune response, interfering with disease pathogenesis and/or reactivation of latent infection. Ulcerative lesion that persisted at a Score of 4 for more than 10 days (it did happen to a few animals), analgesics (buprenorphine 0.1 ml, S.Q. q.d. to b.i.d., and/or bupivacaine topically) were given to the animal as deemed necessary by the veterinarian from day 11 of Score 4. In all cases, animals did not experience clinical signs for more than 3 weeks.

When any of the following occurs, the investigator must be notified, so that, when desired, fresh tissue may be collected by the Principal Investigator or investigators specified in each experiment , and the animal will be euthanized no later than by the close of business on the day of investigator notification by the veterinary staff.

1. **Severe hind limb paralysis that prevents access to food and water.**
2. **Severe foot mutilation including chewing beyond the metatarsal-phalangeal joint, or at the discretion of the facility veterinarian after consultation with the Principal Investigator.**
3. **Secondary bacterial infection as determined by the facility Veterinarian.**
4. **10% body weight loss as compared to non-inoculated littermates (or a guinea pig growth curve).**
5. **A body temperature of less than 97.5 degrees Fahrenheit.**

The investigator will inform the veterinary staff of the commencement of designated Column E studies that include animals that will experience unrelieved pain or distress. This will allow the veterinary staff to ensure appropriate monitoring of animals that are expected to exhibit more than minimal or transient morbidity prior to the experimental endpoint of moribundity. When an animal is found moribund, (immobile, unresponsive to stimuli, or unable to eat or drink), the investigator will be notified immediately. Moribund animals will be euthanized for tissue collection by the investigator on the same day of notification, or by the veterinary staff by close of business the day of investigator notification if the investigator cannot come.

In accordance with animal health monitoring Standard Operating Procedures, animal health observations will be conducted by animal program personnel twice daily on weekdays and once daily on weekends and holidays. The Animal Research Advisory Committee (ARAC) guideline, Endpoints in ASPs, requires that animals showing signs of morbidity be observed twice daily 365 days a year unless an exception is granted by the ACUC. To assist investigators with compliance with the ARAC guideline, the following procedure is employed: If an animal shows signs of morbidity on a Friday, the animal program will notify the investigator conducting the experiment on Friday afternoon in order to either make arrangements for the investigator to euthanize the animal and collect tissues by close of business Friday or for the investigator to perform afternoon observations on the animal(s) on weekends and holidays. The names of personnel to do weekend/holiday monitoring will be clearly posted on the cage cards.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results.

Wild-type HSV infection of guinea pigs causes mucocutaneous lesions, ulcers, and may cause hind-limb paralysis or even death in some animals. To determine if the vaccine candidates can prevent or reduce disease caused by wild-type virus, guinea pigs will be inoculated with vaccine candidates and later challenged with wild-type virus at a dose that can cause disease. We must allow the infection to progress to moribundity so that we can measure the severity of primary disease and the rate of reactivation of HSV over time.

Some animals will have clinical disease that may be painful and/or stressful; unfortunately, treatment with medications will interfere with the interpretation of the experimental results. Analgesic and pain-relieving medicines, including NSAIDS, may alter the immune response to the virus, and therefore may interfere with the outcome. Opiates have also been shown to produce effects on the immune system, such as increasing or decreasing inflammation; opioid analgesics may interfere with virus reactivation (an outcome to be measured) by interacting with receptors on the surface of neurons where the virus maintains in latency.

EXPLANATION FOR COLUMN E LISTING

This form is intended as an aid to completing the Column E explanation. Names, addresses, protocols, veterinary care programs, and the like, are not required as part of an explanation. A Column E explanation must be written so as to be understood by lay persons as well as scientists.

1. Registration Number: **51-F-0016**
2. Number of animals used under Column E conditions in this study. **13** **FY 2005**
3. Species (common name) of animals used in this study. **hamsters**
4. Explain the procedure producing pain and/or distress, including reason(s) for species selected.

   This project is to develop vaccines to protect humans against respiratory viruses, namely highly pathogenic avian influenza viruses. Viral infection and the induction of an immune response can only be studied in living animals. We are limited in our ability to study these virus infections and vaccines responses in the natural human host or in permissive primate models because of limited availability, limited genetic tools, and ethical considerations. Mice, hamsters and ferrets are mammalian models to study disease and evaluate potential vaccine candidates. Avian influenza viruses are not uniformly virulent for mice, hamsters and ferrets. Infection of mice, hamsters and ferrets with some highly pathogenic avian influenza viruses can result in disease symptoms that can range from very mild disease up to pneumonia and even, if unintervened, death. In this regard, it resembles the rare avian influenza infections reported in humans.

5. **Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results.**

   Analgesics. Animals are not expected to experience pain, other than a general malaise in response to influenza virus. NSAIDS (nonsteroidal anti-inflammatory drugs) cannot be used because these drugs produce profound effects on the immune system, such as inhibition of prostaglandin and leukotriene synthesis, and stabilization of lysosomal membranes that may reduce the release of cytokines. These affected systems are important for the immune system processes that are being evaluated in these studies. In vaccine trials, disease progression will be affected by NSAIDS.
   Opiates are not indicated since the pain produced consists of a nonspecific malaise that would likely not be affected by opioids. Many opioids could also increase mortality due to effects on the cardiovascular or respiratory systems. The investigator will notify the facility staff when the animals begin the Column E portion of the study. All animals on the Column E portion of the study will be monitored twice daily including weekends and holidays by animal program staff. The investigator must be contacted when the Column E-study mice are moribund (cold, emaciated, paralyzed, or cachectic with agonal respiration) or the following symptoms and signs are seen in Column C-study mice: dyspnea, hunched posture, cachexia. Animals will be euthanized by the close of business the day of investigator notification when the above clinical signs are seen.

10/20/2005

COLUMN E Explanation Form

This form is intended as an aid to completing the Column E explanation. Names, addresses, protocols, veterinary care programs, and the like, are not required as part of an explanation. A Column E explanation must be written so as to be understood by lay persons as well as scientists.

1 Registration Number: 51-F-0016

2 Number of animals used under Column E conditions in this study: 3

3 Species (common name) of animals used in this study: Rhesus monkeys

4 Explain the procedure producing pain and/or distress, including reason (s) for species selected:
Dorsal lumbar nerve root ligation for neuropathic pain model in the nonhuman primate is extensively published as the nearest model to humans. The DRG is of comprable size and approach is similar and well described in the rhesus monkey.

5 Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results.
The control animals (n = 3) were needed to undergo the exact same lesioning and testing as the experimental animals, only the control would do so without the experimental infusion of resiniferatoxin for pain relief.

EXPLANATION FOR COLUMN E LISTING

This form is intended as an aid to completing the column E explanation. Names, addresses, protocols, veterinary care programs, and the like, are not required as part of an explanation. A column E explanation must be written so as to be understood by lay persons as well as scientists.

1. Registration Number: **51-F-0016**
2. Number of animals used under Column E conditions in this study: **45_FY 2005**
3. Species (common name) of animals used in this study: **Owl monkey**
4. Explain the procedure producing pain/or distress, including reason (s) for species selected.

Animals on this study received Complete Freund's Adjuvant (CFA). Animals given CFA will likely develop granulomatous skin lesions. When these occur, animals are monitored at least twice a day for lethargy, diarrhea, rough hair coat, absence of eating and/or drinking, other clinical signs, and the status of the skin lesions. Skin lesions will be kept clipped and cleaned.
These granulomatous skin lesions may occasionally lead to other lesions due to migration of the CFA into body cavities or other areas. In animals that develop clinical signs indicative of these possible sequellae, diagnostic testing will be performed to rule out anemia, parasitemia, or spontaneous disease, all of which are treatable as discussed in Section F. of the ASP. If moribundity occurs or serious conditions are diagnosed related to the CFA injections, these animals will be treated with appropriate treatments or the animal will be euthanized.

We recently hired a veterinarian who has extensive experience with New World non-human primates, including Aotus. The research branch has teamed up with him and will be working together with the animal facility staff to establish further criteria of how we will treat animals considered to be in pain/distress.

For immunization-challenge studies in non-human primates, CFA is the gold standard against which all other adjuvants must be measured. Vaccine trials at the NIH and in other laboratories have been using CFA for decades in the evaluation of malaria vaccine candidates. One purpose of the trials that we conduct here at NIH and we collaborate on with other investigators at the CDC is to evaluate alternatives to CFA with the hope of one day removing the need for its use in testing vaccine candidates.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results.

The proper treatment for granulomas that become open or problematic is a regimen of systemic antibiotics. Since there may be the possibility that systemic antibiotics could interfere with the replication cycle of the parasites, we will refrain from giving them till after the 28 days the animals are infected. When seen during this period we cleaned the opened granulomas and apply a topical antibiotic/ analgesic. Once the animal is cured and if the opened granulomas still exist, then the animal will be treated topically with antibiotic/analgesic and systemically as well as instructed by the veterinarian.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

NOV 25 2005

November 23, 2005

Elizabeth Goldentyer, D.V.M.
Regional Director - Animal Care
U.S. Department of Agriculture
APHIS Eastern Regional Office
Animal Care Unit No. 304O
920 Main Campus Drive, Suite 200
Raleigh, NC 27606

Dear Dr. Goldentyer:

Enclosed is the National Institutes of Health (NIH) Annual Report of Research Facility as required by the Animal Welfare Regulations. Per your request, all component data is provided as an institutional summary. The attached composite report represents the entire NIH Intramural Research Program.

The following NIH components are covered by this report:

- Thirteen NIH Research Institutes based in Bethesda, Maryland - National Cancer Institute; National Heart, Lung and Blood Institute; National Eye Institute; National Institute of Allergy and Infectious Diseases (including its Rocky Mountain Laboratories (RML) at Hamilton, MT); National Institute of Neurological Diseases and Stroke; National Institute of Child Health and Human Development; National Institute of Diabetes and Digestive and Kidney Diseases; National Institute of Arthritis and Musculoskeletal and Skin Diseases; National Institute of Dental and Craniofacial Research; National Institute on Alcohol Abuse and Alcoholism; National Institute on Deafness and Other Communication Disorders; National Human Genome Research Institute; and the National Institute of Mental Health.

- Two NIH Research Institutes in Baltimore, Maryland - National Institute on Aging and the National Institute on Drug Abuse.

- One other NIH Research Institute in Research Triangle Park, North Carolina - National Institute of Environmental Health Sciences (NIEHS).

- Three NIH Research Centers/Offices in Bethesda, Maryland - the Warren G. Magnuson Clinical Center, Vaccine Research Center, and the Office of Research Services.

- The Alamogordo Primate Facility on the Holloman Air Force Base, New Mexico. This facility is a government-owned contractor-operated entity managed by Charles River Laboratory Company and supported by the National Center for Research Resources.

The NIH-National Cancer Institute contract facility, NCI-Frederick, Frederick, Maryland, is administered separately from the NIH Intramural Research Program and will continue to report independently.

Sincerely,

Michael M. Gottesman, M.D.
Deputy Director for Intramural Research, NIH

Enclosures